DETAILED ACTION

Applicant's election with traverse of the invention of group II comprising claims 14, 15 and 16 in the reply filed on 9/30/2011 is acknowledged.

The traversal is on the bases that the claims also encompass the limitation of a TGFβ comprising a signal sequence wherein the polynucleotide(s) encoding the TGFβ lacks a cysteine in the first 10 amino acids. However addition of a signal sequence to a recombinant proteins for various purposes such as localization of the protein or secretion of the protein were well known at the time of the instant invention. It would therefore have been obvious to include a signal sequence as recited in the claims. Therefore the restriction requirements are maintained. However upon further consideration the invention of group I and II are rejoined as they encompass overlapping subject matter. Claims 17-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected groups, there being no allowable or linking claims. Claims 1-16 are present for examination. The restriction requirements are made final.

Priority

Acknowledgement is made for this application filed on 7/6/2006 which is a national stage application of PCT/US05/00378 filed on 01/06/2005 and claims the benefit of U.S. Provisional Application No. 60534,379, filed 01/06/2004 and 60/575839 filed on 6/02/2004.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is

required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: The oath or declaration does not specify the national stage application PCT/US05/00378 filed on 01/06/2005 for this application neither in the oath or the Application data sheet.

Information Disclosure Statement

The information disclosure statement filed on 04/06/2007 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature.

Specification

The specification is objected to because the first line of the specification must contain cross-reference to related applications. In this case applicants do not claim the benefit of international application PCT/US05/00378 filed on 01/06/2005.

Furthermore, the specification fails to comply with 37 CFR 1.821-1-825 that require for each sequence present in the specification to be assigned a sequence identifier. In the instant case, the requirements are not met because, for example, the TGFβ-1 sequences mentioned on pages 23-24 are not assigned the sequence identifiers. These sequences are represented by GenBank sequence identifiers. However GenBank sequences can change periodically thus sequence identifiers should be provided for these sequences. Appropriate correction is required.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show structural detailes in fig.1 as described in the specification. Any structural detail that is

essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 12 recite the limitation "the regulatory sequence" in reference to claim 4 which ultimately depend on claim 1. There is insufficient antecedent basis for this limitation in the claim. Is this in reference to the signal sequence or other elements in the

polynucleotide sequence the regulatory sequence will be construed as a promoter sequence. For examination purposes Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8-11, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Purchio et al (EP-A-0 373 994 in IDS) in view of Hayasuke et al (EP-A-0 319 641 (June 1989)).

Claims 1-13 encompass are drawn to polynucleotides encoding mammalian pro-TGFβ polypeptides with any structure with the exception that polynucleotides do not encode a cysteine residue within the first ten amino acid residues of the encoded pro-TGFβ and, comprises a heterologous signal sequence. Furthermore these claims encompass

vectors comprising said polynucleotides and method of making the pro-TGF-β polypeptide in eukaryotic host cells. Furthermore said polynucleotide is operably linked a heterologous signal sequence.

Claims 14-16 encompass a polypeptide encoding mammalian pro-TGFβ polypeptide with any structure with the exception that polypeptide does not encode a cysteine residue within the first ten amino acid residues of the pro-TGFβ polypeptide a heterologous signal sequence.

However, Purchio et al (EP-A-0 373 994 in IDS) taught simian TGFβ, a variant simian TGFβ variant where a cysteine to serine mutation at position 33 (which corresponds to position 3 in the pro-TGF-β1 which consists of residues 30-390 under the control of the SV40 expression elements and vectors which contain the entire coding sequence for the simian TGFβ variant obvious over claim 6, 7). The vectors were used to transfect CHO cells which produced and secreted rTGF-β1 and pro-TGF-β1 that retain biological activity comparable to authentic TGF-β1.

Purchio et al taught that the recombinant pro-TGF-β1 which contains a secretory signal sequence was secreted. However, Purchio et al do not specifically teach operably linking a heterologous signal sequence to the polynucleotide encoding the pro-TGFβ. Furthermore Purchio et al do not teach any tag sequence included in the recombinant pro-TGF-β1.

However, providing fusion proteins to facilitate handling of polypeptides were familiar and routine techniques in the art. For example, one of ordinary skill in the art would have been motivated to include a tag sequence such as a His-tag sequence to facilitate purification of the pro-TGF-β1 secreted in the growth media.

Furthermore, with regards to the heterologous signal sequence for secretion of the polypeptide, one of ordinary skill in the art would be motivated to include a signal sequence at the N-terminal portion of the His-tag since inclusion of a tag sequence at the N-terminal of the signal sequence can interfere with the proper function of the endogenous signal sequence. Thus it would have been obvious to one of ordinary skill in the art to include a signal sequence at the N-terminal side of the tag.

Moreover, with regards to heterologous signal sequence, any signal sequence can be included at the N-terminal of the pro-TGF-β1. For example Hayasuke et al (EP-A-0 319 641 (June 1989)) taught the advantages of using an albumin signal sequences operably linked to a foreign/heterologous protein. One of ordinary skill in the art would have a reasonable expectation of success in using Hayashi's albumin signal sequence to express the pro-TGF-β1 comprising an N-terminal tag sequence.

With regards to claim 2, the pro-TGF-β1 taught Purchio et al encompasses the LAP portion.

With regards to claim 3, Purchio et al taught that the simian mature TGF-β1 is 100% identical to the human TGF-β1 and only 5 amino acid variation within the precursor regions of the pro-TGF-β1.

With regards to claim 4 it would have been obvious to obtain the construct the leader, the tag and the pro- TGF-β1 as discussed above.

With regards to claims 5, 10-11, Purchio taught that the vectors comprising encoding the pro-TGF-β1 were used to transfect CHO cells which produced and secreted rTGF-β1 and that the

pro-TGF-β1 that retain biological activity comparable to authentic TGF-β1 (obvious over claim 510-11).

With regards to claims 8, 9 and 12, one of ordinary skill would have constructed a vector that contains the regulatory region in the orientation of the gene to be expressed or would have constructed the regulatory sequence in an antisense orientation depending on the amount of recombinant produced i.e. an antisense orientation would be suitable if overexpression interferes with proper growth or processing of the recombinant TGF-β1. Therefore claims 1-16 would have been prima facie obvious based on the teachings of Purchio et al (EP-A-0 373 994 in IDS) in view of Hayasuke et al (EP-A-0 319 641) absence evidence to the contrary.

Conclusion: No claims are allowed.

Relevant publications:

Lawrence et al US2002/0143165 A1 published on 10/3/2002.

Lawrence et al taught the use of fusion constructs to improve characteristics of the polypeptide. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the final product.

Gentry, .. **and** A. F. Purchio. 1987. Type 1 transforming growth factor beta: amplified expression and secretion of mature and precursor polypeptides in Chinese hamster Ovary cells. Mol. Cell. Biol. 7: 3418-3427.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MANJUNATH RAO can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KAGNEW H GEBREYESUS/
Primary Examiner, Art Unit 1656
December 3, 2011